CORRESPONDENCE

Tumor Necrosis Factor–α Increased Production during Thalidomide Treatment in Patients with Tuberculosis and Human Immunodeficiency Virus Coinfection

To the Editor—We read with interest the article by Bekker et al. [1] on the role of thalidomide-induced antigen-specific immune stimulation in patients with human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* coinfection. In their report, it is suggested that thalidomide treatment of HIV-infected patients does not reduce plasma tumor necrosis factor (TNF)–α levels. The observation is explained by a differential effect of thalidomide on monocyte and T cell TNF-α production. In particular, the authors report that thalidomide inhibited TNF-α production by lipopolysaccharide-stimulated monocytes but failed to inhibit TNF-α production by activated T cells [2–5]. Finally, the authors found an increase in TNF-α production at day 21 of therapy in the thalidomide group, thus suggesting that the drug could be responsible for this increase by stimulation of T cell activation.

As Bekker et al. observed, these data seem to be in contrast with the findings of previous studies, mainly performed in vitro, which reported an anti-inflammatory effect of thalidomide, mediated by an inhibition of TNF-α production [4, 6]. Nevertheless, the data confirm the most recent in vivo reports showing an increase in TNF-α concentrations and soluble TNF-α receptors during thalidomide treatment [7, 8]. These data suggest that thalidomide is not a systemic TNF-α inhibitor. Moreover, it must be underlined that increased TNF-α production in the thalidomide-treated patients was associated with unexplained deaths when thalidomide was used in the treatment of toxic epidermal necrolysis [7].

We conducted a study, similar to the one performed by Bekker and colleagues, using thalidomide to treat HIV- and tuberculosis-coinfected patients. We studied 6 HIV- and *M. tuberculosis*–infected patients, characterized by a poor response to the antituberculosis treatment, who were subsequently treated with thalidomide as adjuvant therapy. Immunological evaluations prior to thalidomide introduction suggested that these patients had significantly lower levels of TNF-α production than did the control subjects. Following thalidomide treatment, we observed a progressive increase in TNF-α production with a peak after about day 35 of therapy, thus confirming the observations made by Bekker and colleagues [1]. The increase in TNF-α concurred with a significant recovery of Th1 cytokine production, such as interleukin-2 and interferon-γ, and was followed by a significant improvement in clinical conditions (reduction of fever, increase in body weight, improvement in radiological findings, and negativization of *M. tuberculosis* cultures) in all patients.

Our data, along with the results of Bekker et al., emphasize the usefulness of thalidomide treatment in patients infected by *M. tuberculosis* and demonstrate the complexity of the immunomodulating effects mediated by this drug. In agreement with the more recent in vivo reports, we confirm that thalidomide did not reduce TNF-α levels, and this is probably due to an activation of T cell activity, as hypothesized by Bekker and colleagues. However, these data raise questions as to the nature of the interaction between TNF-α and thalidomide. In the light of these results, we suggest extreme caution in undertaking studies that support the clinical use of thalidomide, on the basis of the assumption of its contradictory role in TNF-α inhibition.

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Reply

To the Editor—We thank Gori et al. [1] for their letter concerning our recently published article [2]. We have read the letter with great interest. Although we do not have any specific response to the letter, we would like to suggest 3 recently published references relevant to their commentary [3–5].

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